RESEARCH ARTICLE

Mechanochemically Generated Calcium-Based Heavy Grignard Reagents and Their Application to Carbon−Carbon Bond-Forming Reactions

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Abstract: In sharp contrast to the use of conventional magnesium-based Grignard reagents (R−MgX), the application of calcium-based heavy Grignard reagents (R−CaX) in organic synthesis remains poorly explored. This is mainly due to the lack of experimentally simple ways to access such organocalcium nucleophiles from readily available starting materials under mild conditions. Here, we show that a mechanochemical technique using ball milling allows the generation of calcium-based heavy Grignard reagents from aryl halides and commercially available calcium metal without complicated pre-activation processes. Notably, all experimental operations can be carried out in air. Our operationally simple protocol enables the rapid development of novel cross-electrophile-coupling reactions mediated by arylcalcium nucleophiles, which are rather difficult using conventional Grignard reagents. This method will allow synthetic chemists to readily access the novel and unique reactivity of organocalcium nucleophiles.

Introduction

Since Beckmann's pioneering study on the synthesis of an arylcalcium complex more than a century ago,[1] organocalcium compounds have gained significant attention in synthetic chemistry on account of their unique and attractive organic transformations, which have recently been uncovered.[2−4] Their distinct reactivity profile mainly originates from the highly polar calcium−carbon bonds due to the large electronegativity difference between calcium and carbon.[2] However, compared to conventional magnesium-based Grignard reagents (R−MgX)[5], organocalcium species have not been widely used in organic synthesis. One reason for this limitation is the difficulty associated with obtaining a variety of organocalcium compounds via experimentally simple procedures, which hampers practical synthetic applications.[1−4]

Organocalcium compounds are typically prepared via the following methods: (1) Insertion of calcium metal into a carbon−halogen bond (direct synthesis);[6,7] (2) metathesis between CaX_2 and other highly active carbon nucleophiles such as organopotassium or -lithium compounds;[8] (3) deprotonation of acidic C−H bonds by calcium compounds;[9] (4) addition of calcium hydride species to unsaturated carbon−carbon bonds.[3b] Given its broad substrate scope and mild reaction conditions, the direct synthesis from readily available organic halides with calcium metal would seem to be a versatile route to synthetically useful organocalcium reagents, which are known as calcium-based heavy Grignard reagents (R−CaX) (Figure 1a).[6] However, a series of pioneering studies by Westerhausen and co-workers revealed that the low reactivity of calcium metal due to its relatively high atomization energy renders this approach highly challenging.[6i] Therefore, pre-activation of the calcium metal is required prior to its use. One reliable pre-activation method is first dissolving the calcium metal in liquid ammonia and then quickly removing the solvent by distillation at low temperature to provide highly reactive and pyrophoric calcium powder.[6] Rieke calcium metal can also be prepared by reduction of CaX_2 with lithium biphenylide.[2e,3a,6a] Although these activated calcium metals can react with organic halides to form calcium-based heavy Grignard reagents (Figure 1a), the requirements for toxic ammonia or harsh reduction conditions, dry organic solvents, and strict control of the reaction temperature greatly reduce the practical utility of such calcium-based carbon nucleophiles in organic synthesis. Moreover, the complicated experimental procedures required for the pre-activation of calcium may hamper extensive investigations into the reactivity of calcium-based heavy Grignard reagents and result in their basic reactions being overlooked. Therefore, the development of a pre-activation-free, operationally simple protocol for the direct synthesis of calcium-based nucleophiles would be highly desirable to advance the synthetic organic chemistry of organocalcium compounds.

Over the past decade, mechanochemical synthesis using ball milling has attracted significant interest as a powerful method to expand the toolkit of organic chemistry.[10] In particular, the benefits of mechanochemical synthetic techniques have been actively explored in the context of the organometallic chemistry of the main group elements.[11−16] For example, Browne and co-workers have recently reported that a ball-milling approach facilitates the formation of organozinc species via the insertion of metallic zinc into organic halides.[13] More recently, the same group has reported that manganese metal can be activated under ball-milling conditions to promote the reductive dimerization of arylidene malonates.[14] The groups of Harrowfield, Birke, Hanusa, Bolm and our own group have independently reported the mechanochemical activation of magnesium metal for the synthesis of Grignard reagents via the direct insertion of magnesium metal into organic halides without the need for carefully primed solvents.[15,16] Although these achievements are remarkable, the potential of mechanochemistry in the preparation

of novel organometallic reagents from unreactive metals under solution conditions remains unexplored.

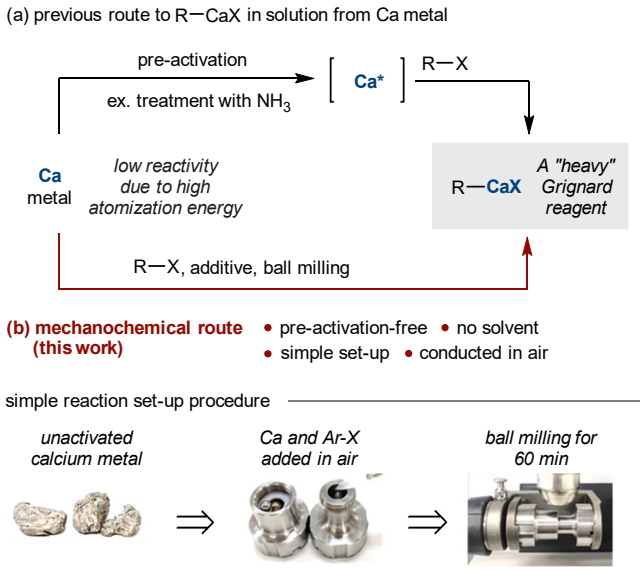


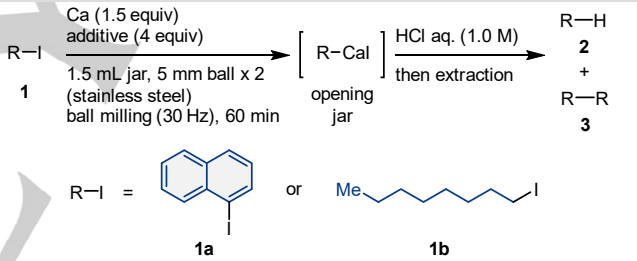
Figure 1. Mechanochemically generated calcium-based heavy Grignard reagents.

Inspired by the synthetic potential of organocalcium nucleophiles[1–4] and the benefits of ball milling for organometallic chemistry,[10–17] we hypothesized that the mechanical impact under ball-milling conditions could provide sufficient energy to overcome the relatively high atomization energy of calcium metal,[6i] which would allow the efficient activation of calcium metal and thus make the direct generation of calcium-based heavy Grignard reagents feasible (Figure 1b). This mechanochemical approach could also potentially represent a powerful and practical strategy for the rapid development of new organic transformations using organocalcium nucleophiles, because it does not require experimentally complicated pre-activation processes using toxic or highly reactive reagents, dry organic solvents, and/or an inert gas atmosphere.

Results and Discussion

All mechanochemical reactions were conducted in a Retsch MM400 ball mill. Firstly, as a proof of concept, we chose 1-iodonaphthalene (**1a**) as a model substrate and added it to a 1.5 mL stainless-steel milling jar with commercially available calcium metal (1.5 equiv relative to **1a**) and two stainless-steel balls (diameter: 5 mm diameter) in air; after ball milling (30 Hz) for 60 min, the mixture was quenched by adding 1.0 M aq. HCl. The reaction of **1a** with calcium metal was evaluated by monitoring the formation of protonation product **2a** (Table 1). Unfortunately, under these conditions, **2a** was formed in only 3% yield (Table 1, entry 1). As ether additives can enhance the thermodynamic stability of organocalcium compounds by coordinating with the metal center,[2,6] we tested the use of tetrahydrofuran (THF) and tetrahydropyran (THP) as additives (4.0 equiv relative to **1a**), which improved the yield of **2a** to 41% and 45%, respectively (Table 1, entries 2 and 3). We also conducted the reaction at a higher temperature (60 °C) using a heat gun (for details, see the Supporting Information),[18] which furnished **2a** in 55% yield (Table 1, entry 4). However, the mass balance did not match, as almost full conversion of **1a** was observed. A MALDI-TOF mass spectrometry analysis of the crude mixture showed multiple peaks corresponding to unidentified oligomeric compounds, which are probably derived from the decomposition of organocalcium species during the reaction (for details, see the Supporting Information). Next, we used 1-iodooctane (**1b**) as the substrate (Table 1, entries 5–8). In contrast to **1a**, the corresponding homo-coupling product **3b** was obtained in high yield, while protonation product **2b** was obtained only as a minor product (Table 1, entries 5–8). These results suggest that the direct insertion of calcium metal into aryl iodides should be feasible under mechanochemical conditions, while alkyl iodides seem to provide predominantly the corresponding homo-coupling product, most likely via Wurtz-type coupling.[6i] This reactivity profile is consistent with conventional solution-based reactions using activated calcium.[6] The appearance of the reaction mixture changed depending on the applied conditions (Figure 2), i.e., ball milling close to room temperature (Table 1, entry 3) produced a sticky yellow oil (Figure 2b), while a waxy black solid (Figure 2c) was obtained after ball milling at 60 °C (Table 1, entry 4).

Table 1. Preliminary study of the generation of organocalcium halides under ball-milling conditions.[a]



entry	R–I	additive	temp. (°C)	recovery of **1** (%)	yield of **2** (%)[b]	Yield of **3** (%)[b]
1	**1a**	none	30	75	3	0
2	**1a**	THF	30	25	41	0
3	**1a**	THP	30	23	45	0
4	**1a**	THP	60	<1	55	0
5	**1b**	none	30	65	6	10
6	**1b**	THF	30	<1	15	66
7	**1b**	THP	30	<1	11	72
8	**1b**	THP	60	<1	15	64

[a] Conditions: **1** (0.5 mmol), Ca (0.75 mmol), THP (2.0 mmol), in a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 5 mm). [b] Determined using GC.

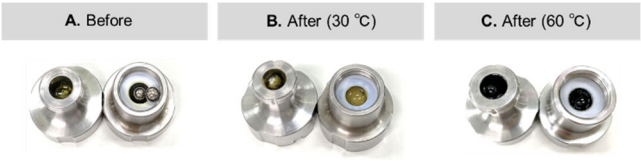
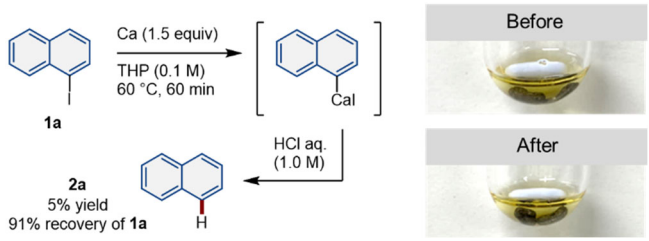


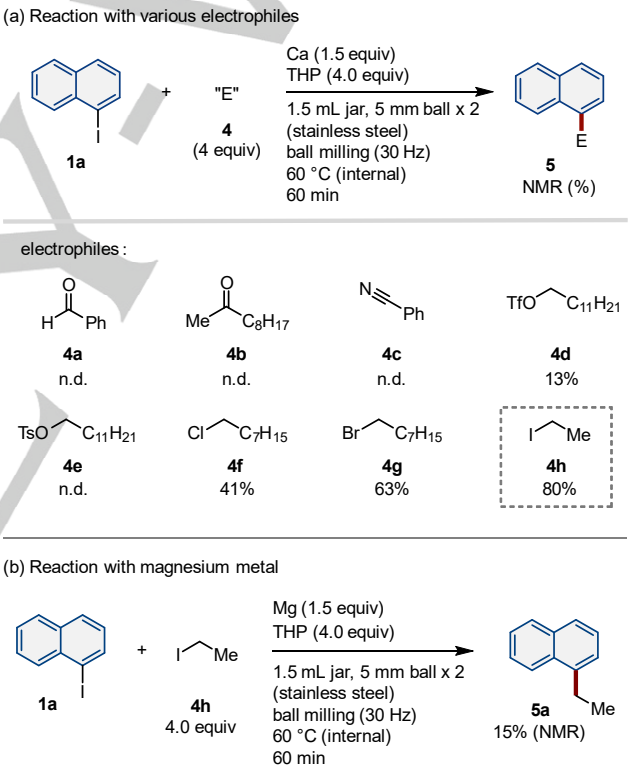
Figure 2. Reaction mixture (A) before ball milling, (B) after ball milling at 30 °C (entry 3, Table 1), and (C) after ball milling at 60 °C (entry 4, Table 1).

To confirm the effectiveness of activation using ball milling, we carried out the reaction between calcium metal and **1a** in THP solution at 60 °C (Scheme 1). Only 5% of the corresponding protonation product **2a** was detected under solution conditions, and a large amount of unreacted calcium metal remained (Scheme 1). This result indicates that the mechanical agitation provided by ball milling plays an essential role in the activation of calcium metal, allowing the generation of the corresponding arylcalcium species.



Scheme 1. Attempts to prepare calcium-based carbon nucleophiles in solution.

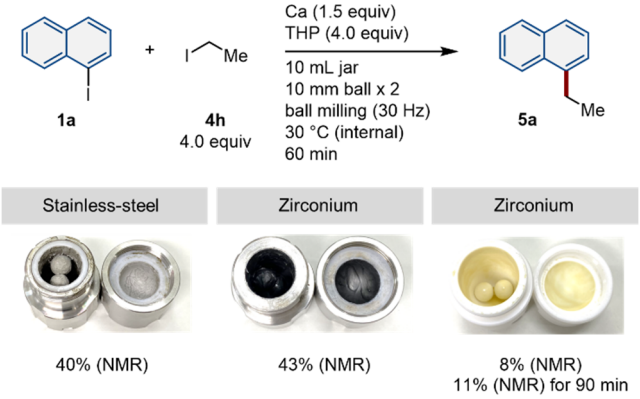
Using this mechanochemical approach, arylcalcium species can be quickly generated from commercially available unactivated calcium metal, which would facilitate the rapid development of new reactions with arylcalcium nucleophiles via screening approaches. With this in mind, we carried out an electrophile screening under mechanochemical conditions (Scheme 2a). When an aldehyde (**4a**) or a ketone (**4b**) were tested as *in-situ* trapping reagents for the formed arylcalcium species, the formation of the desired nucleophilic addition products was not observed. Instead, we confirmed a reduction of the carbonyl group or an aldol reaction. The reaction of benzonitrile (**4c**) resulted in the formation of a complex mixture, and the corresponding triazine was detected via NMR analysis. These results suggest that the reaction of calcium metal with these electrophiles may be faster than the formation of the organocalcium halides. We then turned our attention to the use of alkyl electrophiles. We found that the reaction with alkyl triflate (**4d**), which is an electrophile with high tolerance toward direct reduction, provided the corresponding substitution product in 13% yield. The use of alkyl tosylate (**4e**) did not result in the desired product. Alkyl chloride (**4f**) and alkyl bromide (**4g**) furnished promising results and afforded the corresponding alkylation product (**5a**) in 41% and 63% yield, respectively. The reaction of iodoethane (**4h**) generated **5a** in high yield (80%). It should also be noted here that this is the first example of the alkylation of arylcalcium halides with alkyl electrophiles, and that previous studies on the reactivity of arylcalcium halides prepared via the methods of Westerhausen (activation with liquid NH_3) and Rieke did not explore such simple alkylation reactions.[6] Importantly, the use of magnesium instead of calcium provided a significantly lower yield of **5a** (15%; Scheme 2b), suggesting that the higher nucleophilicity of the arylcalcium nucleophiles compared to that of Grignard reagents facilitates the nucleophilic substitution of unactivated alkyl electrophiles.[2] Preliminary density functional theory (DFT) calculations revealed that Ph–CaI species can be expected to react with Et–I via much lower activation barriers than those in the reaction between Ph–MgI species and Et–I (for details, see the Supporting Information). An energy-decomposition analysis (EDA) and natural-bond-orbital (NBO) calculations suggested that the higher barrier for Ph–MgI is most likely due to the higher distortion energy of the Et–I moiety in the transition state (TS) than in the Ph–CaI case. This is probably due to the larger ionic radius of calcium relative to that of magnesium and to the greater electronegativity difference of the C–Ca bond relative to that of the C–Mg bond, which may facilitate the two-electron transfer from the Ph–CaI species to Et–I and favor the early TS, while the Ph–MgI species favors the late TS, in which the Et–I moiety is more severely distorted.



Scheme 2. Reaction with various electrophiles.

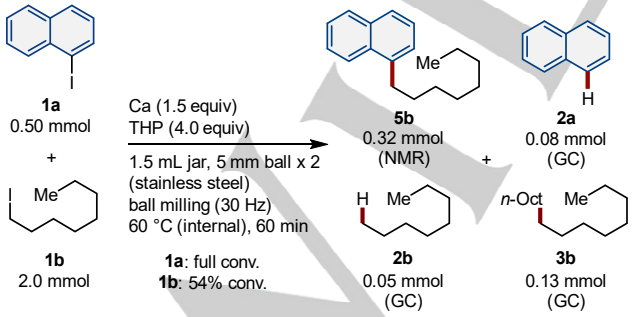
Such cross-electrophile couplings between aryl halides and alkyl halides are commonly catalyzed by transition metals.[19] To discard the possibility that transition metals such as iron and chromium eluted from the stain-less-steel milling jar and/or the balls catalyze the cross-electrophile-coupling reaction, we investigated the reaction using jars made of different materials, such as zirconium oxide or Teflon™ (Scheme 3). Although 1.5 mL is the optimal jar size for this reaction scale, these control reactions were conducted using 10 mL jars and two 10-mm-diameter balls without changing the reaction scale, given that 10 mL was the smallest volume of commercially available jars made of these materials. The results confirmed that the cross-electrophile coupling reactions proceeded regardless of the

material of the milling jars and balls, thus ruling out the possibility of a metal-catalyzed mechanism (Scheme 3). The low yield obtained for the reaction in the Teflon™ jar is probably due to the low mechanical impact provided by the light Teflon™ balls and jar, which is most likely not sufficient to activate the calcium metal.



Scheme 3. Effect of milling jars and balls made of different materials.

To obtain insight into the product selectivity, we analyzed the cross-coupling product/byproducts ratio in the reaction between **1a** (0.50 mmol) and octyl iodide (**1b**; 2.0 mmol) (Scheme 4). Under the optimized conditions, **1a** was fully consumed (0.50 mmol), while the conversion of **1b** was 54% (1.08 mmol). We found that cross-electrophile-coupling product **5b** was obtained in 64% yield (0.32 mmol), and protonation product **2a** was formed (0.08 mmol). The unidentified 0.10 mmol of **1a** was probably converted into the unidentified oligomeric compounds. We also found that both the protonation (**2b**, 0.05 mmol) and homocoupling products (**3b**, 0.13 mmol) of **1b** were generated. As for the conversion of **1b**, 0.31 mmol of **1b** reacted to from **2b** and **3b**, and 0.32 mmol of **1b** was consumed by nucleophilic substitution with the arylcalcium species to form **5b**. The unidentified 0.45 mmol of **1b** would be converted into the unidentified oligomeric compounds. Given that the mechanism of the formation of such oligomeric byproducts is unclear, the selectivity of the activation of aryl and alkyl iodides by calcium cannot be simply discussed based on this result.



Scheme 4. Details of the product selectivity.

Subsequently, we explored the substrate scope of the mechanochemical protocol with a variety of iodoarenes (Table 2). To our delight, a range of substituted iodoaromatics reacted smoothly with iodoethane (**4h**) (Table 2). The reactions of aryl iodides containing electron-neutral substituents (**1c** and **1d**) provided the desired products (**5c** and **5d**) in good yield. Substrates containing an internal alkyne moiety (**1e**) were also tolerated in this protocol. Methoxy (**1f**), thioether (**1g**), and amine (**1h**) groups at the *para* position on the phenyl ring did not affect the reactivity, and the corresponding products (**5e**–**5h**) were obtained in good yield. It should be noted here that the chemoselectivity of this mechanochemical procedure was not affected by a bromine substituent (**1i**), highlighting the potential of this process to be carried out in combination with subsequent conventional cross-coupling transformations. A substrate with a fluorine group (**1j**) was also found to be compatible with the reaction conditions to produce the corresponding product (**5j**) in high yield. Notably, sterically hindered substrates with isopropyl (**1k**), phenyl (**1l**), methoxy (**1m**), or di-substituted-methyl (**1n**) groups at the *ortho*-position of the benzene ring also smoothly furnished the desired products (**5k**–**5n**) in good yield. We also found that the coupling of polycyclic and heterocyclic aromatic motifs (**1o**–**1q**) was possible and furnished the corresponding products (**5o**–**5q**) in moderate to excellent yield. Unfortunately, substrates that contain carbonyl, ester, and amide groups (**1r**–**1t**) resulted in the formation of complex mixtures. Next, a variety of other substituted primary alkyl iodides were tested (Table 2). We found that methylation with methyl iodide (**4i**) smoothly afforded the desired product (**5u**) in good yield. Substrates with longer alkyl chains (**4j**–**4l**) also gave the corresponding products (**5v**–**5x**) in good yield. Functional groups such as chlorine (**4m**), trifluoromethyl (**4n**), silyl ether (**4o**), and an internal alkene (**4p**) did not interfere with this reaction. When secondary or tertiary alkyl iodides were used, alkylation products were not obtained.

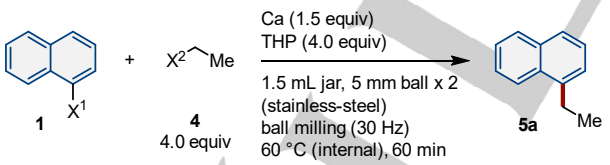
We then investigated combinations of different types of organic halides (Table 3). We found that alkyl bromides can also be used as alkylation reagents, and the corresponding product (**5a**) was obtained in good yield (entry 1). In the reaction between 2-naphthyl bromide (**1u**) and bromoethane (**4q**), the yield of **5a** was moderate (entry 2). The reaction between **1u** and iodoethane **4h** provided **5a** in only 18% yield (entry 3). Given that 48% of **1u** remained unreacted after the reaction, we speculate that the activation of a carbon–bromine bond in **1u** by the calcium metal is relatively slow and the preferential activation of **4h** may proceed to induce undesired side reactions such as Wurtz-type coupling.

Finally, we tested solution-based reactions of an arylcalcium halide formed via insertion using activated calcium metal (Scheme 5). The Rieke method using lithium biphenylide[6a] was applied to the cross-electrophile coupling, and the desired alkylation product (**5a**) was obtained in 54% yield. We also used calcium metal activated by ammonia[6] for this reaction, which provided **5a** in 22% yield. These results suggest that similar calcium-based heavy Grignard reagents of aryl species (Ar–CaX) are most likely formed under mechanochemical conditions, and subsequently undergo nucleophilic substitution with the alkyl electrophiles to form the cross-electrophile coupling products.[20]

Table 2. Substrate scope with respect to aryl/alkyl iodides.[a]

[a] Unless otherwise noted, all mechanochemical reactions were conducted in a Retsch MM400 mill (stainless-steel milling jar; 30 Hz; stainless-steel balls). Conditions: **1** (0.5 mmol), **2** (2.0 mmol), Ca (0.75 mmol), THP (2.0 mmol), in a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 5 mm), heat gun set to 120 °C, ball milling (30 Hz) for 60 min. NMR yields were determined by ^{1}H NMR analysis using dibromomethane as an internal standard. Isolated yields are given in brackets. [b] 1.5 equiv of **4i** was used and the heat gun was set to 80 °C.

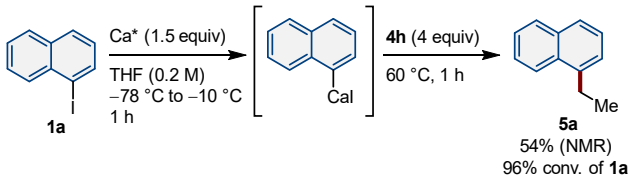
Table 3. Combinations of other types of electrophiles.



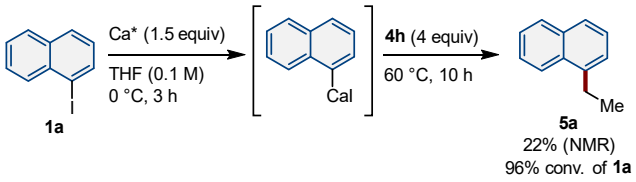
entry	X1	X2	Yield of **5a** (%)[a]
1	I (**1a**)	Br (**4q**)	79 (61)
2	Br (**1u**)	Br (**4q**)	47
3	Br (**1u**)	I (**4h**)	18

[a] NMR yields were determined by ^{1}H NMR analysis using dibromomethane as an internal standard. Isolated yields are shown in parentheses.

(a) Use of Rieke Ca for a substitution reaction in solution



(b) Use of Ca activated by ammonia for a substitution reaction in solution



Scheme 5. Reactions using activated calcium metal in solution.

Conclusion

In summary, using the presented mechanochemical method, we have achieved for the first time the generation of calcium-based heavy Grignard reagents (Ar–CaX) from commercially available, unactivated calcium metal without applying any pre-activation process. Furthermore, we present the first example of the alkylation of arylcalcium nucleophiles with alkyl electrophiles to form carbon−carbon bonds, which has not been reported using previous pre-activation methods for the direct generation of organocalcium compounds. As noted, the developed mechanochemical protocol does not require any laborious pre-activation steps, the employment of toxic and/or strong reducing reagents, the use of inert gas, or dry organic solvents, which allows the entire procedure to be conducted in air. This operational simplicity suggests that the present study can be expected to open the door for synthetic chemists to explore the novel and unique reactivity of organocalcium nucleophiles more easily. Beyond the immediate benefits of this ball-milling approach in organocalcium chemistry, the present study showcases the outstanding potential of mechanochemistry for the preparation of novel organometallic compounds that are difficult to access by other means.

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Keywords: calcium • ball mill • mechanochemistry • cross-electrophile coupling • solid-state reaction

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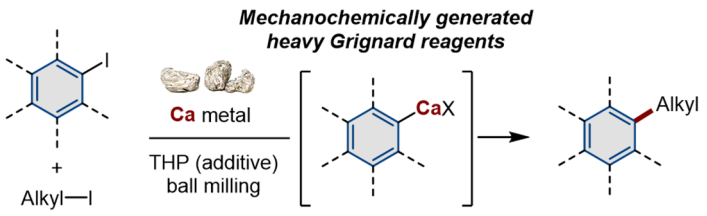

Using a mechanochemical technique, we have achieved for the first time the generation of calcium-based heavy Grignard reagents (Ar–CaX) from commercially available, unactivated calcium metal without applying any pre-activation process. Our operationally simple protocol enables the rapid development of novel cross-electrophile-coupling reactions mediated by arylcalcium nucleophiles under mechanochemical conditions.